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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,616	11/12/2003	Jing Huang	3533.1	2187

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EXAMINER	
AGRAWAL, RITESH	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,616	HUANG ET AL.	
	Examiner	Art Unit	
	Ritesh Agrawal	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *23-25 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,26-33 and 35-39* is/are rejected.

7)☒ Claim(s) *2,4,5,6,7,12,26-29,30,31,32,33,37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/18/04, 06/02/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I and the species of numerical anomaly for claim 15 in the replies filed on 07/05/06 and 09/11/06 is acknowledged.

Claims 23-25 and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 07/05/06.

Information Disclosure Statement

2. The Information Disclosure Statements filed 06/18/04 and 06/02/06 have been entered and considered. Initialed copies of the form PTO-1449 are enclosed with this action.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

The Zip Code change for applicant Jing has not been dated.

Specification

4. The disclosure is objected to because of the following:

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

The abstract of the disclosure is objected to because the abstract is not drawn to the elected invention, namely, a method for determining DNA copy number. Furthermore, whereas the claims are drawn to a method, the abstract does not provide any method steps. Additionally, the abstract provides speculative applications of the method. Correction is required. See MPEP § 608.01(b).

The use of the trademarks GENECHIP, AMPLITAQ GOLD, PICOGREEN, and QIAAMP have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. GENECHIP can be found, for

example, on page 12 of the specification. QIAAMP can be found on page 49 of the specification and AMPLITAQ GOLD and PICOGREEN can be found on page 50 of the specification.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-22, 26-33, and 35-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "from the value obtained in (e)" in line 21. This phrase is indefinite since there are multiple values obtained in (e). These values include the S value and the intensities of perfect match probes. It is unclear as to which of these values the phrase refers.

Claim 2 recites the limitation "the autosomal SNPs" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 3 recites the limitation "the estimated copy number alteration" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 3 recites the limitation "the estimated direction of copy number change" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 4 recites the limitation "the estimated copy number alteration" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 4 recites the limitation "the estimated direction of copy number change" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation "the normalized S values" in line 5. There is insufficient antecedent basis for this limitation in the claim.

Claim 9 recites the limitation "the direction of estimated copy number alteration" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 10 recites the phrase "equal to about." This is indefinite since the term "equal to" usually represents a defined number. The modification of the term with "about" renders the term indefinite.

Claim 11 recites the limitation "the direction of estimated copy number alteration" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 11 recites the limitation of an equation for the calculation of p-value in line 3. There is insufficient antecedent basis for this limitation in the claim. The different variables used in the equation are not defined.

Claim 18 recites the limitation of an equation defining DR in line 5. There is insufficient antecedent basis for this limitation in the claim. The equation terms are not defined in the claim or the claim from which it depends.

Claim 19 recites the limitation "the direction of change for the SNP" in line 13. There is insufficient antecedent basis for this limitation in the claim.

Claim 26 recites the limitation "the SNPs in the identified region" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 28 recites the limitation of an equation for the calculation of p-value in line 2. There is insufficient antecedent basis for this limitation in the claim. The different variables used in the equation are not defined.

Claim 30 recites the limitation "the direction of change" in line 17. There is insufficient antecedent basis for this limitation in the claim.

Claim 32 recites the limitation of an equation for calculating p-value in line 2. There is insufficient antecedent basis for this limitation in the claim. The different variables used in the equation are not defined.

Claim 33 recites the limitation of an equation for calculating copy number in line 2. There is insufficient antecedent basis for this limitation in the claim. The different variables used in the equation are not defined.

Claims 35-39 are indefinite for being drawn to multiple statutory classes; an apparatus and a process.

Claim 35 recites the limitation "the direction of change" in line 17. There is insufficient antecedent basis for this limitation in the claim.

Claim 37 recites the limitation of an equation for the calculation of p-value in line 2. There is insufficient antecedent basis for this limitation in the claim. The different variables used in the equation are not defined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-7, 12-15, 17, 19-20, and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindblad-Toh et al. (IDS, Nature Biotechnology, Vol. 18, Pages 1001-1005, September, 2000) in view of Zhou et al. (BMC Bioinformatics, Vol. 3,

January 2002) and further in view of Draghici (Drug Discovery Today, Vol. 7, Pages S55-63, June 2002) and further in view of Kaminski et al. (American Journal of Respiratory Cell and Molecular Biology, Vol. 27, Pages 125-132, August, 2002).

The claims are drawn to a method for estimating the copy number of a genomic region comprising:

(a) isolating nucleic acid

(b) amplifying some regions of the nucleic acid

(c) labeling the amplified product

(d) hybridizing the amplified products to an array containing perfect match and mismatch probes directed towards SNPs

(e) obtaining a measurement for the SNP in an experimental sample and calculating an S value as the log of the arithmetic value of the intensities of at least two perfect match probes

(f) obtaining an S value from reference samples

(g) calculating a mean and standard deviation for the reference sample values

(h) obtaining a log intensity difference by subtracting the mean value obtained for the reference samples from the mean value obtained for the experimental sample

Lindblad-Toh et al. disclose a method of estimating copy number in a genomic region using a microarray which genotypes SNPs (page 1001, 1st column, 1st paragraph, lines 9-14) where they isolate, amplify, label, and hybridize nucleic acid samples (page 1001, 1st column, 2nd paragraph, line 6-9 – page 1001, 2nd column, 1st paragraph, lines 1-2). They disclose that the probes on the array consist of perfect-

match and mismatch probes (page 1001, 2nd column, 1st paragraph, lines 3-7). The reference therefore discloses steps (a)-(d) of applicant's method.

Lindblad-Toh et al. are silent, however, on the ways in which the data obtained from the raw microarray experiments are manipulated other than stating that they used Affymetrix Genechip software (paragraph 1004, 1st column, 3rd paragraph, lines 3-5). They therefore do not disclose steps (e)-(h) of the method.

Zhou et al. disclose calculating an average difference between perfect match and mismatch intensities on a given microarray (page 14, 1st column, 3rd paragraph, line 6). They also disclose the comparison of a reference sample with an experimental sample by calculating a ratio between the average difference in an experimental sample versus the average difference in a control sample (page 14, 2nd column, 3rd paragraph, lines 3-6). Furthermore, Zhou et al. disclose eliminating the mismatch intensity in carrying out calculations (page 2, 1st column, 3rd paragraph, lines 4-6) thereby calculating a ratio of the average of perfect match intensity values between an experimental sample and a reference sample.

It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method of Lindblad-Toh et al. to use the algorithm of Zhou et al. One of ordinary skill in the art would have been motivated to do so, because, as suggested by Zhou et al., this allows for doubling of the chip information density (page 2, 1st column, 3rd paragraph, line 7) and provides for better results (for example, see figure 1).

However, while the teachings of Zhou et al. and Lindblad-Toh et al. disclose calculating a ratio of average perfect match intensities, they do not disclose calculating a log intensity difference.

Draghici teaches carrying out a log transformation of data (page S56, 1st column, 1st paragraph, lines 8-9), where, in particular, they calculate a log of gene expression ratios (page S57, 1st column, 1st paragraph, line 7).

It would have been obvious for one of ordinary skill in the art, at the time the invention was made, to modify the combined method of Zhou et al. and Lindblad-Toh et al. with the log transformation of Draghici. One of ordinary skill in the art would have been motivated to do so because, as suggested by Draghici, doing so would improve the ability to carry out statistics on the data (page S56, 1st column, 1st paragraph, lines 9-10).

The combined teachings of Lindbadh-Toh, Zhou, and Draghici therefore provide for calculating the log of the ratio of the average perfect match intensity values between an experimental sample and a reference sample. Since the log of a ratio between a numerator and a denominator is equal to the difference between the log of the numerator value (the S-value for the experimental sample) and the log of the denominator value (the S-value for the reference sample), this provides for the calculation of the log intensity difference value when there is a single reference and a single experimental sample.

However, the combination of the Lindbadh-Toh, Zhou, and Draghici references does not disclose calculating obtaining a log intensity difference when there are a plurality of reference samples.

Kaminski et al. disclose using multiple samples and calculating a representative value for the multiple samples as the mean of the multiple samples (figure 2, legend, part (A)).

It would have been obvious for one of ordinary skill in the art, at the time the invention was made, to combine to modify the combined method of Lindbadh-Toh, Zhou, and Draghici such that it was carried out using multiple samples and, as such, the log intensity difference was calculated as the difference between the S-value for the experimental sample and the average S-value for reference samples. One of ordinary skill in the art would have been motivated to do so, because, as highlighted by Kaminski, the results from a single sample are less accurate and not necessarily representative of the results one obtains when using multiple samples (see pages 128, 1st column, 1st paragraph, lines 13-16 and column, line 1 along with page 129, 1st column, 1st paragraph, lines 1-5). Despite the fact that the combined references do not specifically teach calculating the standard deviation of multiple reference samples, it would have been obvious to one of ordinary skill in the art to do so since calculating the standard deviation when multiple values are involved in an experiment is commonplace (see, for example, Draghici et al., page S57, 1st column, 1st paragraph, lines 8-9).

With respect to step (i), Lindbadh-Toh et al. calculate the copy number (page 1003, 1st column, 2nd paragraph, lines 3-4). Since the reference is silent as to what

assumption they used in calculating copy number from gene expression levels, there is no reason to believe they did not assume a linear relationship given that such a relationship was known in the art (See IDS Reference, Pinkel et al., Nature Genetics, Vol. 20, Pages 207-211, fig. 1).

With respect to claim 2, it simply represents a Z-normalization of the data which is disclosed by Zhou et al. (page 9, 2nd column, 2nd paragraph, lines 3-7).

With respect to claims 3 and 4, Kaminski et al. disclose calculating p-values and using thresholds of such values to assess statistical significance of expression changes (see, for example, figure 2, legend, lines 9-10). While Kaminski et al. apply this to the expression levels themselves rather than a change in copy number, the copy number is being calculated as a linear function of the expression level so application of p-value thresholds to expression level changes would necessarily apply it to copy number changes.

With respect to claim 5, since the S-value is being calculated as the log of the average perfect match intensity value, it is being calculated as per the equation.

With respect to claims 6 and 7, Zhou et al. disclose the use of 20 probes (page 8, 1st column, 2nd paragraph, lines 7-8).

With respect to claim 12, Lindbadh-Toh disclose the measuring of copy number in tumor samples (see, for example, title).

With respect to claims 13 and 14, Lindbadh-Toh disclose that tumor (experimental samples) can contain normal cells, and therefore, their experimental

sample is from a non-cancerous sample and is a mixture (page 1002, 1st column, 3rd paragraph).

With respect to claim 15, Lindbadh-Toh et al. disclose their suspicion of chromosomal numerical anomalies (page 1003, 1st column, 2nd paragraph, lines 2-3).

With respect to claim 17, the Affymetrix software (which was used by Lindblad-Toh) automatically filters probes with gene expression values greater than 3 standard deviations from the mean as part of its data quality metrics (see, for example, Wodicka et al., Nature Biotechnology, 15, 1359-1367, page 1366, 2nd column, 2nd paragraph, lines 14-17). Since the S-value is proportional to the gene expression values, removing the probes with intensities greater than 3 standard deviations from the mean also removes S-values greater than 3-standard deviations from the mean.

With respect to claims 19-20, they represent methods combining the methods of claims 1-5. Since the references set forth in this action teach each of the methods as a combined method (as cited above) they teach claims 19-20.

With respect to claims 30-31, the references set forth in this action disclose an associated method. Furthermore, Zhou et al. specifically disclose computer software products (MAS4 and MOID) for analysis of gene expression data (see, for example, abstract). Just as it would have been obvious to modify the methods of Zhou et al. it would have been obvious to modify their software programs to carry out those methods.

Claim Objections

7. Claim 2 is objected to because of the following informalities: The claim uses the word "wherin" in line 1. Appropriate correction is required.

Claim 12 is objected to because of the following informalities: The claim uses the term "methof". Appropriate correction is required.

Claims 26-29 are objected to because of the following informalities: The claims are dependent from a withdrawn claim. Appropriate correction is required.

Claims 30-33 are objected to because of the following informalities: Claim 30 recites the phrase "a computer readable media". Appropriate correction is required.

Claim 32 is objected to because of the following informalities: The claim recites the phrase "p valued". Appropriate correction is required.

Claim 37 is objected to because of the following informalities: The claim recites the phrase "p valued". Appropriate correction is required.

Conclusion

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ritesh Agrawal whose telephone number is (571) 272-2906. The examiner can normally be reached on 8:30 AM - 5:00 PM M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ritesh Agrawal RA

10/15/06